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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
90337.147501		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US01/46841	08 NOVEMBER 2001	08 NOVEMBER 2000
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/74 and US Cl.: 424/78.04		
Applicant BIO-CONCEPT LABORATORIES		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 JUNE 2002	21 SEPTEMBER 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Dorothea Lawrence for CARLOS AZPURU
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/46841

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/46841

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-7	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-7	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-7	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-7 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the instant contact lens solution comprising 0.001 to 10 weight percent or a preservative enhancer chosen from the group consisting of thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), and cobalamin (B12); and at least 0.001 weight percent of a cationic polymeric preservative and a concentration of a 0.2 or less percent chloride. The instant contact lens solution has industrial applicability as a contact lens cleaning solution.

NEW CITATIONS

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 2-9, filed with the letter of 06 June 2002.

This report has been drawn on the basis of the claims,
page(s) NONE, as originally filed.
page(s) NONE. as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
page 10, filed with the letter of 06 June 2002.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application Serial Nos. 60/246,689, filed November 8, 2000, 60/246,707, filed November 8, 2000, 60/246,708, filed November 8, 2000, and 60/246,709, filed November 8, 2000.

Field of the Invention

The present invention relates to the field of ophthalmic solutions and their uses. In particular the invention relates to contact lens cleaning solutions, contact lens rinsing and storing solutions, solution to deliver active pharmaceutical agents to the eye, solutions for disinfecting ophtalmic devices and the like.

Background

The present invention relates to the field of ophthalmic solutions and especially to the aspects of preservative efficacy and comfort after prolonged use. These ophthalmic solutions have been used for some period of time and are available as over the counter products. Solutions that are used in direct contact with corneal tissue such as the delivery of active pharmaceutical agent to the eye, or indirectly, such as the cleaning, conditioning or storage of devices that will come in contact with corneal tissue, such as contact lenses, there is a need to insure that these solution do not introduce sources of bacterial or other microbial infection. Thus preservatives are included to reduce the viability of microbes in the solution and to lessen the chance of contamination of the solution by the user since many of the solutions are bought, opened, used, sealed and then reused.

State of the art preservative agents include polyhexamethylene biguanide (phmb), polyquad [tm], chlorhexidine, and benzalkonium chloride, and the like, all of which at some concentration irritate corneal tissue and lead to user discomfort. Therefore, a solution that employs a given amount of a preservative agent, but which is made

more effective by addition of an agent that is not a preservative agent would be desired.

Summary of the Invention

The present invention relates to improved ophthalmic solutions that employ select B vitamins; pyridoxine and its salts; and thiamine and its salts in order to more effectively preserve solutions and to reduce the degree to which cationic preservatives will deposit on contact lenses. Ophthalmic solutions are here understood to include contact lens treatment solutions, such as cleaners, soaking solutions, conditioning solutions and lens storage solutions, as well as wetting solutions and in-eye solutions for treatment of eye conditions.

Detailed Description

The solutions specifically described herein have 0.001 to about 1 percent of select B vitamins; pyridoxine and its salts; and thiamine and its salts in combination with other active ingredients useful in ophthalmic solutions such as tonicity agent, buffers, preservatives, surfactants, and antimicrobial agents.

The B family of vitamins includes of thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), and cobalamin (B12) . While each form of B vitamin is chemically distinct, they are often found in the same nutritional sources and hence deficiency in one is often related to deficiency in a the other forms. Metabolically, they work with one another to bolster metabolism, enhance immune and nervous system function, maintain healthy skin and muscle tone, and promote cell growth and division. They may also relieve stress, depression, and cardiovascular disease. A deficiency in one B vitamin often means that intake of all B vitamins is low which is why B as a nutritional source are often provided in multivitamin or B-complex formulae.

Niacin contributes to a great number of bodily processes. Among other things niacin helps convert food into energy, build red blood cells, synthesize hormones, fatty-acids and steroids. The body uses niacin in the process of releasing energy from

carbohydrates. Niacin is also needed to form fat from carbohydrates and to process alcohol. Niacin also helps regulate cholesterol.

Pyridoxine is needed to make serotonin, melatonin, and dopamine. Vitamin B-6 is an essential nutrient in the regulation of mental processes and possibly assists in mood and many other health concerns

Cobalamin is needed for normal nerve cell activity. Vitamin B-12 is also needed for DNA replication, and production of the mood-affecting substance called SAMe (S-adenosyl-L-methionine). Vitamin B-12 works with folic acid to control homocysteine levels. An excess of homocysteine, which is an amino acid (protein building block), may increase the risk of heart disease, stroke, and perhaps osteoporosis and Alzheimer's disease.

Other compounds such as folic acid or folate are active in combination with the B vitamins and are needed to synthesize DNA. DNA allows cells to replicate normally. Folic acid is especially important for the cells of a fetus when a woman is pregnant. Folic Acid is also needed to make SAMe and keep homocysteine levels in the blood from rising. Folic Acid (pteroylglutamic acid) is not active as such in the mammalian organism, but rather is enzymatically reduced to tetrahydrofolic acid (THFA), the coenzyme form. An interrelationship exists with vitamin B12 and folate methabolism that further involves vitamin B6: folate coenzymes participate in a large number of metabolic reactions in which there is a transfer of a one-carbon unit.

Pantothenic Acid, also sometimes referred to as coenzyme A, is the physiologically acitive form of pantothenic acid, and serves a vital role in metabolism as a coenzyme for a variety of enzyme-catablyzed reactions involving transfer of acetyl (two-carbon) groups. Surprisingly, pantothenic acid is essential for the growth of various microorganisms, including many strains of pathogenic bacteria.

In the form of contact lens rinsing solutions and/or pharmaceutical agent delviery system the solutions will contain, in addition to the lens or the pharmaceutical agent 0.0001 to about 1.0 weight percent of one of the vitamin B forms or a vitamin B co-metabolite chosen from the group consisting of thiamine (B1), riboflavin (B2), niacin

(B3), pantothenic acid (B5), pyridoxine (B6), and cobalamin (B12), folic acid, carnitine.

The preservatives that are specifically useful are cationic preservatives such as polyhexamethylene biguanide (phmb), polyquad [tm], chlorhexidne, and benzalkonium chloride, as well as other cationic preseratives that may prove useful in the present invention as well. The cationic preservatives are used at effective amounts as preservatives, and in the instance of PHMB from 0.0001 percent by weight to higher levels of about 0.01 weight percent.

It was found that an unexpected preservative efficacy was displayed when inositol was used in conjunction with the cationic preservative. The other components of the solution are used at levels known to those skilled in the art in order to improve the wearability of lenses and when used directly in the eye, to provide increased resistance to infection. Inositol and other simple saccharides used in ophthalmic solutions increases preservative efficacy in certain formulations, provides increased resistance to infection in corneal tissue, in certain formulations, and improves the quality of tears in certain formulations.

The formulations may also include buffers such as phosphates, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine

Surfactants that might be employed include polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and polyethoxylated castor oils, but preerrably the polyethoxylated castor oils. These surfactants are commercially available. The polyethoxylated castor oils are sold by BASF under the trademark Cremaphor.

The solutions of the present invention may contain other additives including but not limited to buffers, tonicity agents, demulcents, wetting agents, preservatives, sequestering agents (chelating agents), surface active agents, and enzymes.

Other aspects include adding to the solution from 0.001 to 1 weight percent chelating agent (preferably disodium EDTA) and/or additional microbicide, (preferably 0.00001

to 0.1 or 0.0000 1 to 0.01) weight percent polyhexamethylene biquanide (PHMB0, N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium- 1, hexetidine, bronopol, alexidine, low concentrations of hydrogen peroxide, and ophthalmologically acceptable salts thereof

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or water-soluble salts thereof, including ethylenediaminetetraacetic acid, nitrilotriacetic acid, diethylenetriamine pentaacetic acid, hydroxyethylethylenediaminetriacetic acid, 1,2-diaminocyclohexanetetraacetic acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' tetraacetic acid (EGTA), aminodiacetic acid and hydroxyethylamino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tn- and tetra-sodium salts of ethylenediaminetetraacetic acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include citric acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphates, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and potassium salts as well as the ammonium salt.

The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.0 to 7.6. Significant deviations from neutral (pH 7.3) will cause changes in the physical parameters (i.e. diameter) in some contact lenses. Low pH (pH less than 5.5) can cause burning and stinging of the eyes, while very low or very high pH (less than 3.0 or greater than 10) can cause ocular damage.

The additional preservatives employed in the present invention are known, such as polyhexamethylene biguanide, N-alkyl-2-pyrrolidone, chlorhexidine, polyhexamethylenebiguanide, alexidine, polyquaternium- 1, hexetidine, bronopol and

a very low concentration of hydrogen peroxide, e.g., 30 to 200 ppm.

The solutions of the invention are compatible with both rigid gas permeable and hydrophilic contact lenses during storage, cleaning, wetting, soaking, rinsing and disinfection.

A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and viscosity inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include sodium chloride, potassium chloride, glycerol or mixtures thereof The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.2 weight percent sodium chloride. The important factor is to keep the concentrations of such additives to a degree no greater than that would supply a chloride concentration of no greater than about 0.2 mole percent.

Suitable viscosity inducing agents can include lecithin or the cellulose derivatives such as hydroxymethylcellulose, hydroxypropylcellulose and methylcellulose in amounts similar to those for surfactants, above.

EXAMPLE 1 Pyridoxine

Formulations containing pyridoxine HCl (Spectrum) and Thiamine HCl (Fisher) were prepared in a 0.2% phosphate buffer. The solutions were made isotonic with sodium chloride and preserved with polyhexamethylene biquanide at 0.0001%. The pH was adjusted to 7.2 with either 1 N sodium hydroxide or 1 N hydrochloric acid. The *in vitro* microbicidal activity of the solutions was determined by exposing *C. albicans* to 10 ml of each solution at room temperature for 4 hours. Subsequently, an aliquot of each solution was serial diluted onto agar plates and incubated for 48 hours at elevated temperatures. At the conclusion of the incubation period the plates are examined for the development of colonies. The log reduction was determined

based on a comparison to the inoculum control. The following table provides the results of the in vitro studies.

Additive	4 Hour Log Reduction
Pyridoxine HCl (0.5%)	2.0
Buffer Control	0.8

The solution containing pyridoxine HCl and thiamine HCl showed an improvement in the activity against *C. albicans* as compared to the buffer control.

2. Patent: Expanded Thiamine and Pyridoxine (B Vitamins and B Vitamin Precursors)

Example 2 Formulations containing dexpanthenol

Formulations containing dexpanthenol were prepared in a 0.2% phosphate buffer. The solutions were made isotonic with sodium chloride and preserved with polyhexamethylene biquanide at 0.0001%. The pH was adjusted to 7.2 with either 1 N sodium hydroxide or 1 N hydrochloric acid. The *in vitro* microbicidal activity of the solutions was determined by exposing *C. albicans* to 10 ml of each solution at room temperature for 4 hours. Subsequently, an aliquot of each solution was serial diluted onto agar plates and incubated for 48 hours at elevated temperatures. At the conclusion of the incubation period the plates are examined for the development of colonies. The log reduction was determined based on a comparison to the inoculum control. The following table provides the results of the *in vitro* studies.

Log Reduction	Buffer	Preservative	Electrolyte	Additive
2.16	none	PHMB 0.0001%	none	None
3.41	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	Dexpanthenol

This data shows that the dexpanthenol has improved preservative efficacy over a solution with a preservative alone.

What is claimed is:

1. A contact lens solution comprising 0.001 to 10 weight percent or a preservative enhancer chosen from the group consisting of thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), and cobalamin (B12); and at least 0.0001 weight percent of a cationic polymeric preservative and a concentration of 0.2 or less percent chloride.

2. The contact lens solution of claim 1, wherein the concentration of said cationic polymeric preservative is between 1 and 100 parts per million.

3. The contact lens solution of claim 1, further comprising a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

4. The contact lens solution of claim 1, further comprising between 0.01% and 5.0% glycerin.

5. The contact lens solution of claim 1 further comprising between 0.01% and 2.0% of decanedioic acid.

6.. The contact lens solution of claim 1 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and polyethoxylated castor oils.

7. The contact lens solution of claim 1 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.